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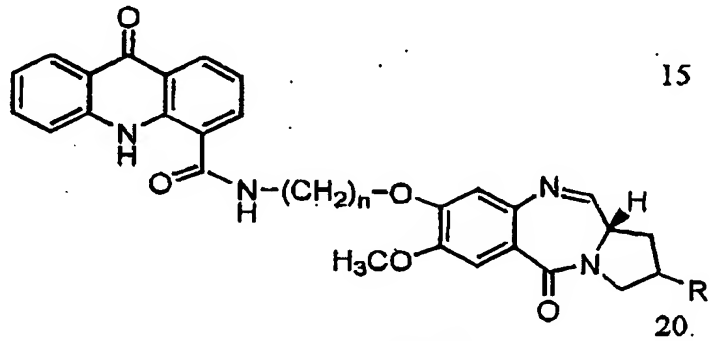
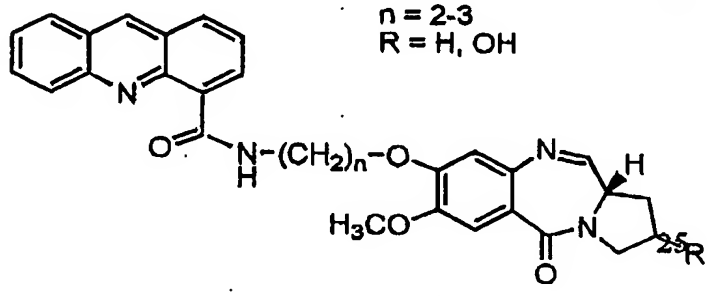
C8 – LINKED PYRROLO[2,1-*c*][1,4]BENZODIAZEPINE-ACRIDONE/ACRIDINE HYBRIDS

Field of the invention

The present invention provides novel pyrrolo-[2,1-*c*][1,4]benzodiazepine hybrids useful as anti-tumour agents. The present invention also provides a process for the preparation of new pyrrolo[2,1-*c*][1,4]benzodiazepine hybrids as antitumour agents. More particularly, the present invention provides a process for the preparation of 7-methoxy-8-[n'-(4"-acridonylcarboxamido)alkyl]-oxy-(11a*S*)-1,2,3,11a-tetraydro-5*H*-pyrrolo[2,1-*c*] [1,4]benzodiazepin-5-one and 7-methoxy-8-[n'-(4"-acridinylcarboxamido)-alkyl]-oxy-(11a*S*)-1,2,3,11a-tetraydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one with aliphatic chain length variation of these compounds and it also describes the DNA binding, anticancer (antitumour) activity. The structural formula of the novel pyrrolo[2,1-*c*]-[1,4]benzodiazepines of the invention is given below:



n = 2-3
R = H, OH

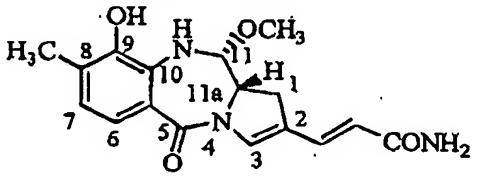


n = 2-3
R = H, OH

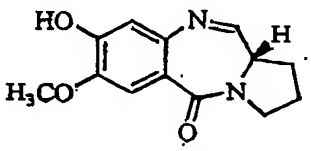
Background of the invention

Pyrrolo[2,1-*c*][1,4]benzodiazepine antitumour antibiotics are commonly known as anthramycin class of compounds. In the last few years, a growing interest has been shown in the development of new pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs). These antibiotics react covalently with DNA to form an N2-guanine adduct that lies within the minor groove of duplex DNA *via* an acid-labile aminal bond to the electrophilic imine at the N10-C11 position (Kunimoto, S.; Masuda, T.; Kanbayashi, N.; Hamada, M.; Naganawa, H.;

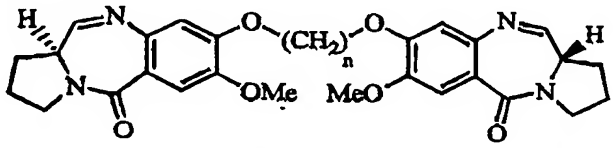
Miyamoto, M.; Takeuchi, T.; and Unezawa, H. *J. Antibiot.*, **1980**, *33*, 665.; Kohn, K. W. and Speous, C. L. *J. Mol. Biol.*, **1970**, *51*, 551.; Hurley, L. H.; Gairpla, C. and Zmijewski, M. *Biochem. Biophys. Acta.*, **1977**, *475*, 521.; Kaplan, D. J. and Hurley, L. H. *Biochmestry*, **1981**, *20*, 7572). The molecules have a right-handed twist, which allows them to follow the curvature of the minor groove of B-form double-stranded DNA spanning three base pairs. A recent development has been the linking of two PBD units through their C-8 positions to give bisfunctional alkylating agents capable of cross-linking DNA (Thurston, D. E.; Bose, D. S.; Thomson, A. S.; Howard, P. W.; Leoni, A.; Croker, S. J.; Jenkins, T. C.; Neidle, S. and Hurley, L. H. *J. Org. Chem.*, **1996**, *61*, 8141).



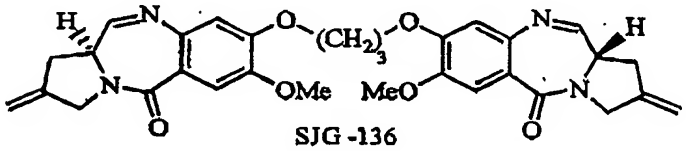
anthramycin



DC-81



DC-81 dimers (n = 3-5); DSB-120 (n = 3)



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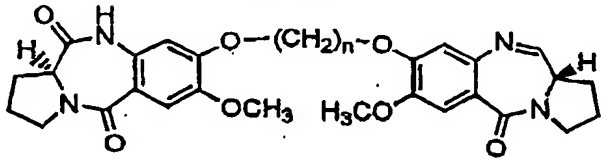


imine-amide PBD dimers; n = 3 - 5

Recently, PBD dimers have been developed that comprises two C2-exo-methylene substituted DC-81 subunits tethered through their C-8 position via an inert propanedioxy linker (Gregson, S. J.; Howard, P. W.; Hartely, J. A.; Brooks, N. A.; Adams, L. J.; Jenkins, T. C.; Kelland, L. R. and Thurston, D. E. *J. Med. Chem.* **2001**, *44*, 737). Recently, a noncross-linking mixed imine-amide PBD dimers have been synthesized that have significant DNA binding ability and potent antitumour activitiy. (Kamal, A.; Ramesh, G.; Laxman, N.; Ramulu, P.; Srinivas, O.; Neelima, K.; Kondapi, A. K.; Srinu, V. B.; Nagarajaram, H. M. *J. Med. Chem.* **2002**, *45*, 4679).

Naturally occurring pyrrolo[2,1-*c*][1,4]benzodiazepines belong to a group of antitumour antibiotics derived from *Streptomyces* species. Recently, there is much impetus for the PBD systems as they can recognize and bind to specific sequence of DNA. Examples of naturally occurring PBD's include anthramycin, DC-81, tomaymycin, sibiromycin and neothramycin.

However, the clinical efficacy for these antibiotics is hindered by several limitations, such as poor water solubility, cardiotoxicity, development of drug resistance and metabolic inactivation.

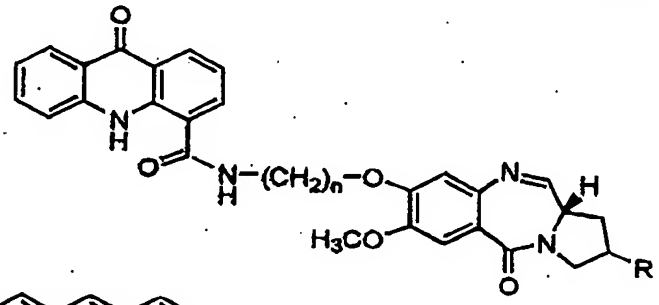
Objects of the invention

The main object of the present invention is to provide new pyrrolo[2,1-*c*][1,4]-benzodiazepine hybrids useful as antitumour agents.

Another objective of the present invention is to provide a process for the preparation of novel pyrrolo[2,1-*c*][1,4]-benzodiazepine hybrids useful as antitumour agents.

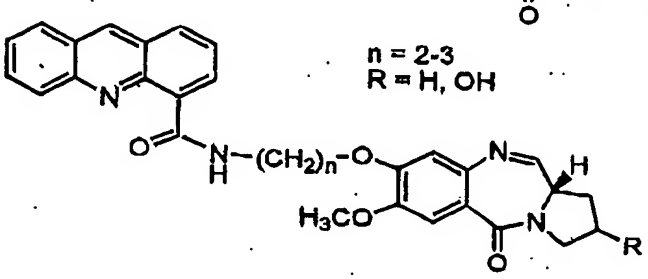
Summary of the invention

Accordingly the present invention provides novel pyrrolo[2,1-*c*][1,4]benzodiazepine hybrids of formula IV or VII wherein R = H, OH and n is 2-3.



Formula IV

n = 2-3
R = H, OH



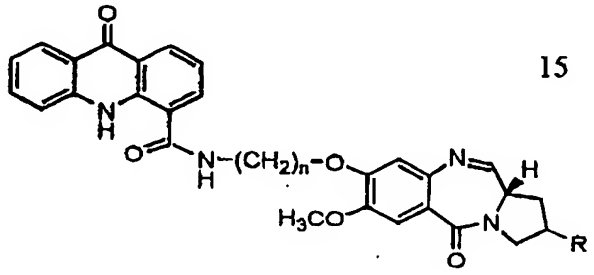
Formula VII

n = 2-3
R = H, OH

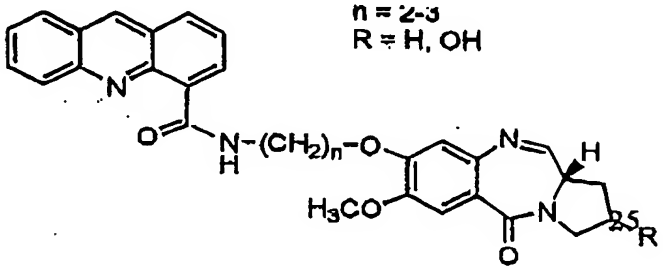
In one embodiment of the invention, the compound of the invention is selected from the group consisting of 7-Methoxy-8-[2'-(4"-acridonylcarboxamido)ethyl]-oxy-(11a*S*)1,2,3,11a-tetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one; 7 – Methoxy – 8 -[2' - (4" – acridonylcarboxamido) ethyl] – oxy - (4*R*) – hydroxy - (11a*S*) 1, 2, 3, 11a-

tetrahydro - 5*H* – pyrrolo [2, 1-*c*] [1, 4] benzodiazepin – 5 – one; 7-Methoxy-8-[3'-(4"-acridonylcarboxamido)propyl]-oxy-(11a*S*)1,2,3,11a-tetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4] benzodiazepin-5-one; 7-Methoxy-8-[3'-(4"-acridonylcarboxamido)propyl]-oxy-(4*R*)-hydroxy -(11a*S*)1,2,-3,11a tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one; 7-Methoxy-8-[2'-(4"-acridinylcarboxamido)ethyl]-oxy-(11a*S*)1,2,3,11a-tetrahydro-5*H*-pyrrolo [2,1-*c*][1,4]benzodiazepin-5-one; 7-Methoxy-8-[2'-(4"-acridinylcarboxamido)ethyl]-oxy-(4*R*)-hydroxy-(11a*S*)1,2,3,-11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one; 7-methoxy – 8 - [3'-(4"-acridinylcarboxamido)propyl]-oxy-(11a*S*)1,2,3,11a-tetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one and 7-Methoxy-8-[3'-(4"-acridinylcarboxamido) propyl]-oxy-(4*R*)-hydroxy-(11a*S*)1,2,-3,11a tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one.

The present invention also provides a process for preparation of pyrrolo-[2,1-*c*][1,4]benzodiazepine hybrids of formula IV and VII wherein R = H, OH and n is 2-3,

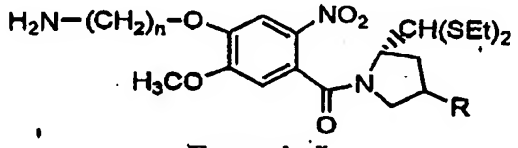


Formula IV



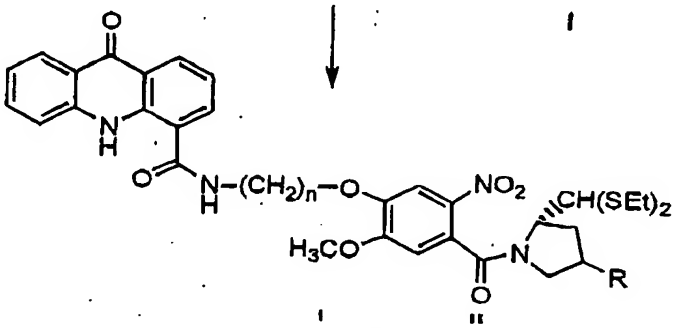
Formula VII

the process comprising reacting an acridone or an acridine acid with (2*S*)-N-[4-(n'-aminoalkyloxy)-5-methoxy-2-nitrobenzoyl]-pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula I

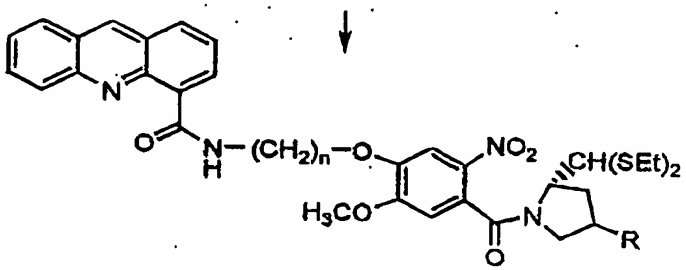


Formula I

in the presence of EDCI and HOBt in organic solvent for a period of 24 h to obtain (2*S*)-N-{4-[n'-(4"-acrido-nylcarboxamido)-alkyl]-oxy-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal II / (2*S*)-N-{4-[n'-(4"-acridinylcarboxamido)-alkyl]-oxy-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula V where 'n' is 2-3,

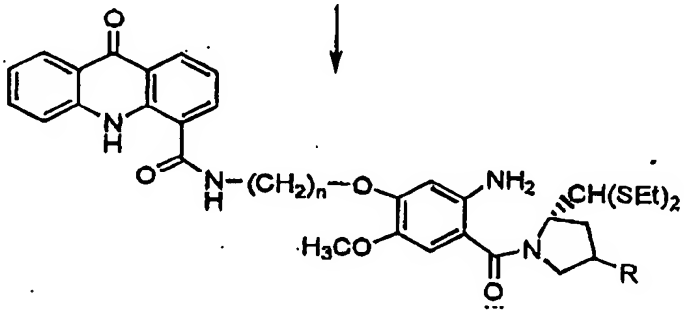


Formula II

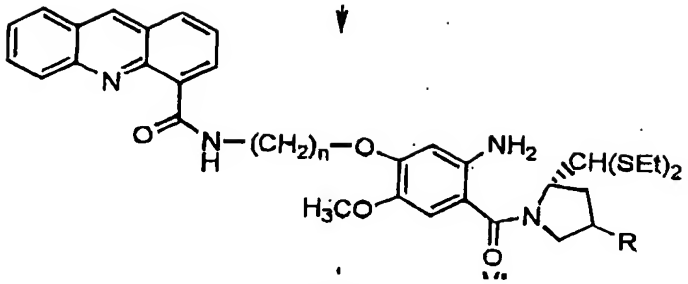


Formula V

isolating the compound of formula II/formula V and then reducing the compounds of formula II/formula V with $SnCl_2.2H_2O$ in presence of an organic solvent up to a reflux temperature, isolating the (2*S*)-N-{4-[n'-(4"-acridonylcarboxamido)-alkyl]-oxy-5-methoxy-2-aminobenzoyl}pyrroli-dine-2-carboxaldehydediethylthioacetal of formula III/(2*S*)-N-{4-[n'-(4"-acridinylcarbox-amido)-alkyl]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula VI where n is 2-3 by known methods,



Formula III



Formula VI

reacting compound of formula III/formula VI with a known deprotecting agents in a conventional manner to give novel pyrrolo[2,1-*c*][1,4]benzodiazepine hybrids of formula IV/formula VII wherein n and R are as stated above.

In one embodiment of the invention, the organic solvent used for the reaction of the acridone/acridine acid with compound of formula I comprises dimethyl furan.

In another embodiment of the invention, the compound of formula II/formula V is isolated by washing with saturated $NaHCO_3$, brine, drying and evaporation of the solvent.

In another embodiment of the invention the organic solvent used during the reduction of compound of formula II/formula V comprises methanol.

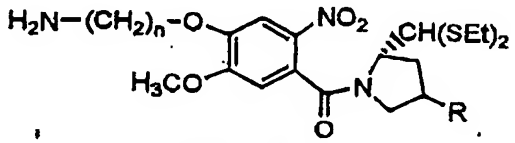
In a further embodiment of the invention, the compound of formula III/formula V is isolated by adjusting the pH of the reaction mixture to about pH 8 with a saturated $NaHCO_3$ solution, diluting with ethyl acetate, filtering through celite and extracted an organic phase and drying the organic phase over Na_2SO_4.

In another embodiment of the invention, the deprotecting agent used for obtaining the compound of formula IV/formula VII comprises $HgCl_2$ and $CaCO_3$ in MeCN-water (4:1).

Detailed description of the invention

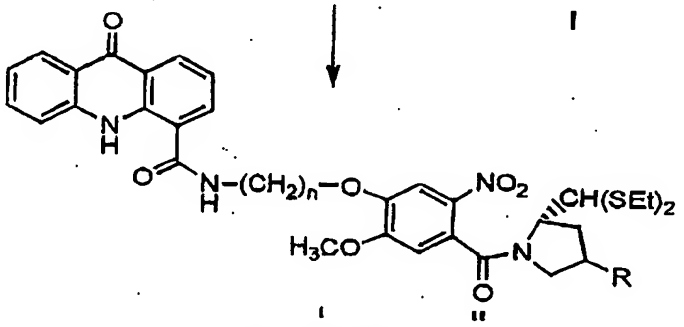
The present invention provides novel pyrrolo[2,1-*c*][1,4]benzodiazepine hybrids of formula IV or VII wherein R = H, OH and n is 2-3 and also provides a process for the preparation thereof.

The process of the invention comprises reacting an acridone or an acridine acid with (2*S*)-N-[4-(n'-aminoalkyloxy)-5-methoxy-2-nitrobenzoyl]-pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula I

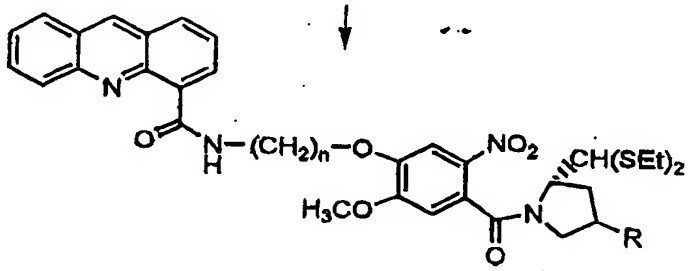


Formula I

in the presence of EDCI and HOBt in organic solvent for a period of 24 h to obtain (2*S*)-N-{4-[n'-(4"-acrido-nylcarboxamido)-alkyl]-oxy-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal II / (2*S*)-N-{4-[n'-(4"-acridinylcarboxamido)-alkyl]-oxy-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula V where n is 2-3,

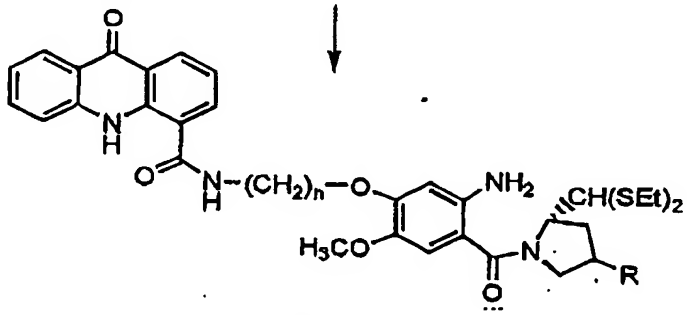


Formula II

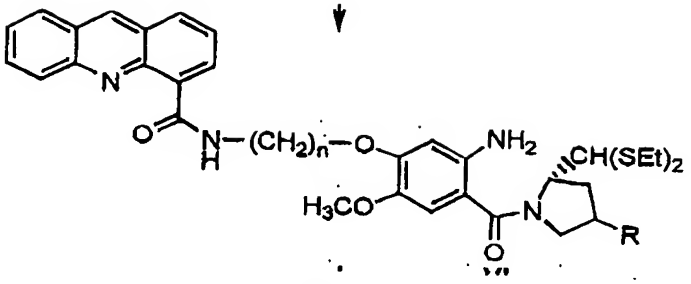


Formula V

The compound of formula II/formula V is isolated and then reduced with $SnCl_2.2H_2O$ in the presence of an organic solvent such as methanol up to a reflux temperature to obtain (2*S*)-N-{4-[n'-(4"-acridonylcarboxamido)-alkyl]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehydediethylthioacetal of formula III/(2*S*)-N-{4-[n'-(4"-acridinylcarboxamido)-alkyl]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula VI where n is 2-3. The compounds of formula III/formula VI are then isolated by conventional methods.

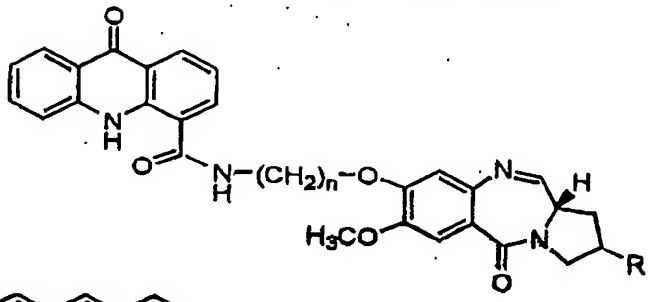


Formula III



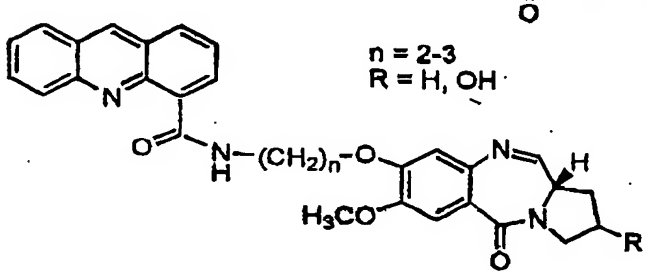
Formula VI

The compounds of formula III/formula VI with a known deprotecting agents in a conventional manner to give novel pyrrolo[2,1-*c*][1,4]benzodiazepine hybrids of formula IV/formula VII wherein n and R are as stated above



Formula IV

n = 2-3
R = H, OH



Formula VII

n = 2-3
R = H, OH

The organic solvent used for the reaction of the acridone/acridine acid with compound of formula I comprises dimethyl furan and the compound of formula II/formula V is isolated by washing with saturated $NaHCO_3$, brine, drying and evaporation of the solvent. The organic solvent used during the reduction of compound of formula II/formula V comprises methanol and the compound of formula III/formula V is isolated by adjusting the pH of the reaction mixture to about pH 8 with a saturated $NaHCO_3$ solution, diluting with ethyl acetate, filtering through celite and extracted an organic phase and drying the organic phase over Na_2SO_4.

The deprotecting agent used for obtaining the compound of formula IV/formula VII comprises $HgCl_2$ and $CaCO_3$ in MeCN-water (4:1).

The precursors, acridone acid (Atwell, G. J.; Cain, B. F.; Baguley, B. C.; Finlay, G. J.; Denny, W. A. *J. Med. Chem.* **1984**, *27*, 1481), acridine acid (Atwell, G. J.; Rewcastle, G. W.;

Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **1987**, *30*, 664) and (2*S*)-N-[4-(n□-aminoalkyloxy)-5-methoxy-2-nitrobenzoyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula I (Thurston, D. E.; Morris, S. J.; Hartley, J. A. *Chem. Commun.* **1996**, 563-565) have been prepared by literature methods.

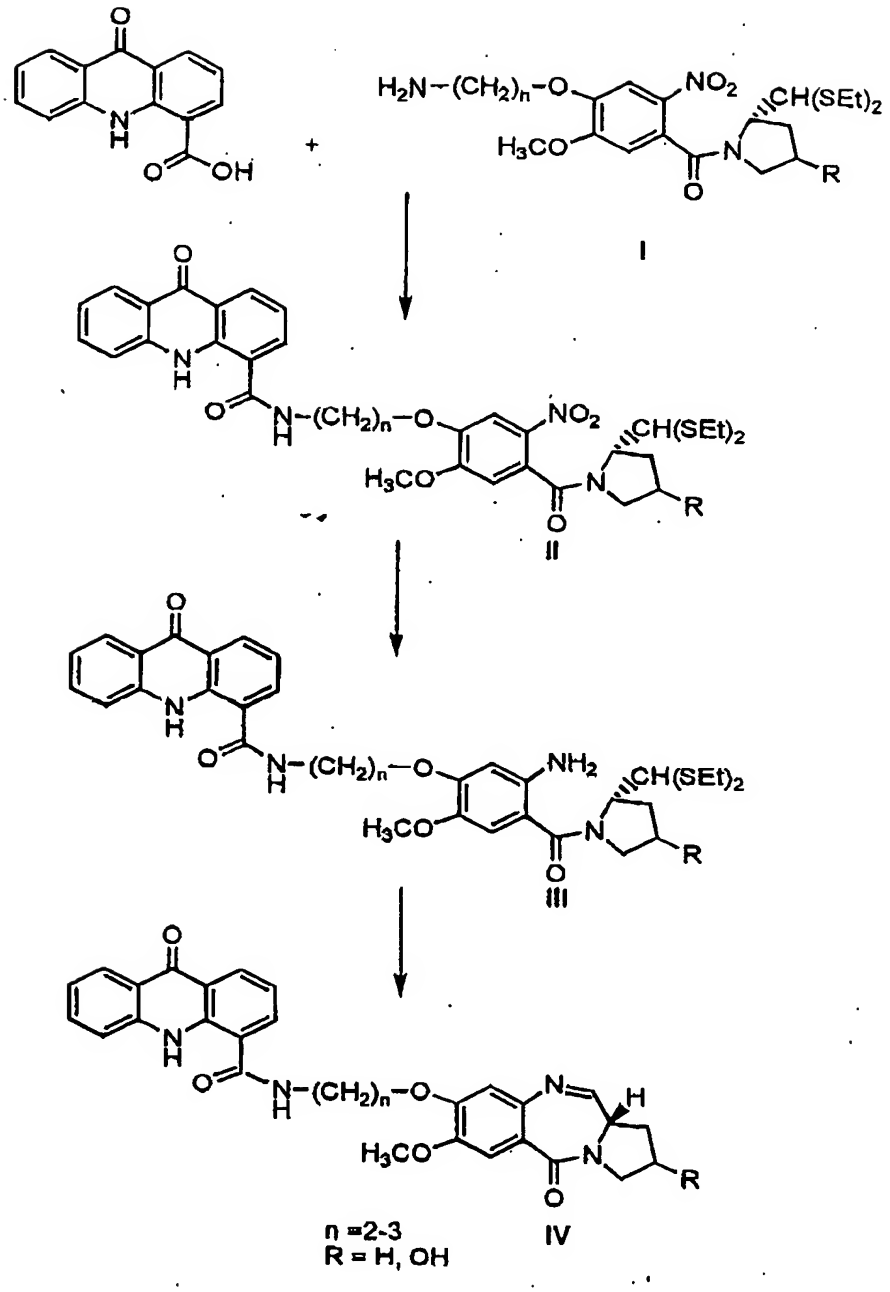
Some representative compounds of formula IV/VII present invention are given below

1. 7-Methoxy-8-[2'-(4"-acridonylcarboxamido)ethyl]-oxy-(11a*S*)1,2,3,11a-tetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one
2. 7-Methoxy-8-[2'-(4"-acridonylcarboxamido)ethyl]-oxy-(4*R*)-hydroxy-(11a*S*)1,2,-3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one
3. 7-Methoxy-8-[3'-(4"-acridonylcarboxamido)propyl]-oxy-(11a*S*)1,2,3,11a-tetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one
4. 7-Methoxy-8-[3'-(4"-acridonylcarboxamido)propyl]-oxy-(4*R*)-hydroxy-(11a*S*)1,2,-3,11a tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one
5. 7-Methoxy-8-[2'-(4"-acridinylcarboxamido)ethyl]-oxy-(11a*S*)1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one
6. 7-Methoxy-8-[2'-(4"-acridinylcarboxamido)ethyl]-oxy-(4*R*)-hydroxy-(11a*S*)1,2,3,-11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one
7. 7-Methoxy-8-[3'-(4"-acridinylcarboxamido)propyl]-oxy-(11a*S*)1,2,3,11a-tetra-hydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one
8. 7-Methoxy-8-[3'-(4"-acridinylcarboxamido)propyl]-oxy-(4*R*)-hydroxy-(11a*S*)1,2,-3,11a tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one

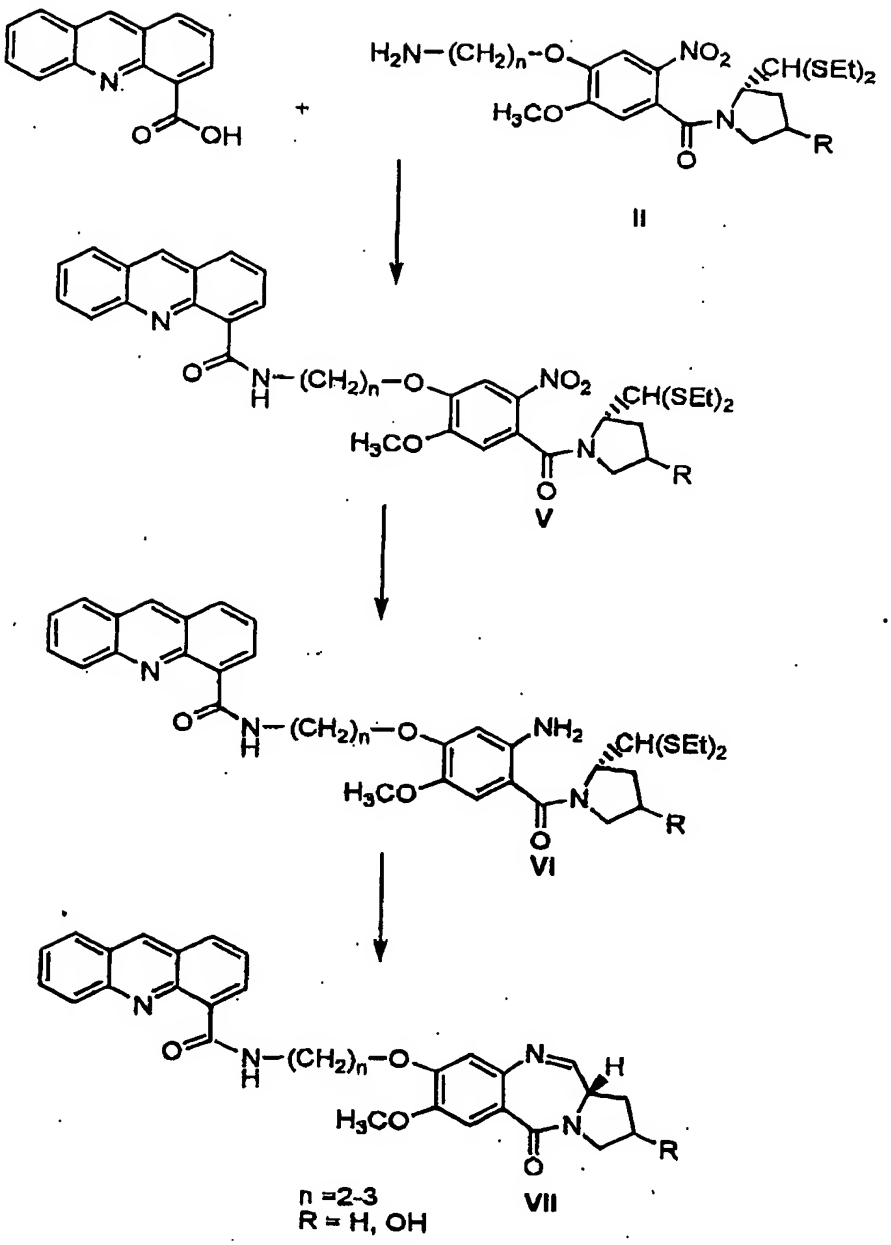
These new analogues of pyrrolo[2,1-*c*][1,4]benzodiazepine hybrids linked at C-8 position have shown promising DNA binding activity and efficient anticancer activity in various cell lines. The molecules synthesized are of immense biological significance with potential sequence selective DNA-binding property. This resulted in design and synthesis of new congeners as illustrated in **Scheme-1/Scheme-2,** which comprise:

1. The ether linkage at C-8 position of DC-81 intermediates with acridone/acridine ring moiety.
2. Up to refluxing the reaction mixture for 12-48 h.
3. Synthesis of C-8 linked PBD antitumour antibiotic hybrid imines.
4. Purification by column chromatography using different solvents like ethyl acetate, hexane, dichloromethane and methanol.

The reaction schemes are given below and are representative of the process of the invention.



Scheme 1



Scheme 2

The following examples are given by way of illustration and therefore should not be construed to the present limit of the scope of invention.

Example 1

Compound acridone acid (0.239 g, 1 mmol) was taken in dry DMF (10 mL), EDCI (0.203g, 1.5 mmol) and HOBt (0.288 g, 1.5mmol) was added and the mixture was cooled at 0-5 °C and the mixture was stirred for 30 min. A solution of (2*S*)-N-[4-(2□-aminoethyl)-oxy-5-methoxy-2-nitrobenzoyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula I (0.443 g, 1mmol) in DMF was added to it at the same temperature and the solution was

stirred at room temperature for overnight. The mixture was washed with saturated $NaHCO_3$ (50 mL), brine, dried and solvent was evaporated. The crude material was chromatographed over silicagel using ethylacetate/hexane (8:2) solvent to give compound (2*S*)-N-{4-[2'-(4"-acridonylcarboxamido)-ethyl]-oxy-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal II as a yellow liquid.

The compound (2*S*)-N-{4-[2'-(4"-acridonylcarboxamido)-ethyl]-oxy-5-methoxy-2-nitro-benzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal II (0.664 g, 1 mmol) was dissolved in methanol (15 mL) and added $SnCl_2.2H_2O$ (1.128 g, 5 mmol) was refluxed for 2 h or until the TLC indicated that reaction was completed. The reaction mixture was then adjusted to pH 8 carefully with saturated $NaHCO_3$ solution, diluted with ethyl acetate, filtered through celite and extracted. The combined organic phase was dried over Na_2SO_4, and evaporated under vacuum to afford the crude compound (2*S*)-N-{4-[2'-(4"-acridonylcarboxamido) - ethyl] – oxy – 5 – methoxy – 2 - aminobenzoyl} pyrrolidine – 2 - carboxaldehyde diethyl thioacetal III.

A solution of compound (2*S*)-N-{4-[2'-(4"-acridonylcarboxamido)-ethyl]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal III (0.634 g, 1 mmol), $HgCl_2$ (0.8145 g, 3 mmol) and $CaCO_3$ (0.3 g, 3 mmol) in MeCN-water (4:1) was stirred slowly at room temperature until TLC indicates complete loss of starting material. The reaction mixture was diluted with EtOAc (30 mL) and filtered through a celite bed. The clear yellow organic supernatant was extracted with saturated 5% $NaHCO_3$ (20 mL), brine (20 mL) and the combined organic phase is dried (Na_2SO_4). The organic layer was evaporated in vacuum and purified by column chromatography (90% CH_2Cl_2-MeOH) to give compound 7-methoxy-8-[2'-(4"-acridonylcarboxamido)ethyl]-oxy-(11a*S*)1,2,3,11a-tetrahydro-5*H*-pyrrolo [2,1-*c*][1,4]benzodiazepin-5-one.

Example 2

Compound acridone acid (0.239 g, 1 mmol) was taken in dry DMF (10 mL), EDCI (0.203g, 1.5 mmol) and HOBt(0.288 g, 1.5mmol) was added and the mixture was cooled at 0-5 °C and the mixture was stirred for 30 min. A solution of (4*R*)-hydroxy-(2*S*)-N-[4-(2'-aminoethyl)-oxy-5-methoxy-2-nitrobenzoyl]pyrrolidine-2-carboxaldehyde diethylthioacetal of formula I (0.459 g, 1 mmol) in DMF was added to it at the same temperature and the solution was stirred at room temperature for overnight. The mixture was washed with saturated $NaHCO_3$ (50 mL), brine, dried and solvent was evaporated. The crude material was chromatographed over silica gel using ethyl acetate/hexane (8:2) solvent to give (4*R*)-

hydroxy-(2*S*)-N-{4-[2'-(4"-acridonylcarboxamido)-ethyl]-oxy-5-methoxy-2-nitrobenzoyl} pyrrolidine-2-carboxaldehyde diethyl thioacetal II as a yellow liquid.

The compound (4*R*)-hydroxy-(2*S*)-N-{4-[2'-(4"-acridonylcarboxamido)-ethyl]-oxy-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal II (0.680 g, 1 mmol) was dissolved in methanol (15 mL) and added $SnCl_2.2H_2O$ (1.128 g, 5 mmol) was refluxed for 2 h or until the TLC indicated that reaction was completed. The reaction mixture was then adjusted to pH 8 carefully with saturated $NaHCO_3$ solution, diluted with ethyl acetate, filtered through celite and extracted. The combined organic phase was dried over Na_2SO_4, and evaporated under vacuum to afford the crude compound (4*R*)-hydroxy-(2*S*)-N-{4-[2'-(4"-acridonylcarboxamido)-ethyl]-oxy-5-methoxy-2-aminobenzoyl}-pyrrol-idine-2-carboxaldehyde diethyl thioacetal III.

A solution of compound (4*R*)-hydroxy-(2*S*)-N-{4-[2'-(4"-acridonylcarboxamido)-ethyl]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal III (0.650 g, 1 mmol), $HgCl_2$ (0.8145 g, 3 mmol) and $CaCO_3$ (0.3 g, 3 mmol) in MeCN-water (4:1) was stirred slowly at room temperature until TLC indicates complete loss of starting material. The reaction mixture was diluted with EtOAc (30 mL) and filtered through a celite bed. The clear yellow organic supernatant was extracted with saturated 5% $NaHCO_3$ (20 mL), brine (20 mL) and the combined organic phase is dried (Na_2SO_4). The organic layer was evaporated in vacuum and purified by column chromatography (90% CH_2Cl_2-MeOH) to give compound 7-methoxy-8-[2'-(4"-acridonylcarboxamido)-ethyl]-oxy-(4*R*)-hydroxy-(11a*S*)1,2,3,-11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiaze-pin-5-one.

Example 3

Compound acridone acid (0.239 g, 1 mmol) was taken in dry DMF (10 mL), EDCI (0.203 g, 1.5 mmol) and HOBt (0.288 g, 1.5mmol) was added and the mixture was cooled at 0-5°C and the mixture was stirred for 30 min. A solution of (2*S*)-N-[4-(3'-aminopropyl)-oxy-5-methoxy-2-nitrobenzoyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula I (0.457 g, 1 mmol) in DMF was added to it at the same temperature and the solution was stirred at room temperature for overnight. The mixture was washed with saturated $NaHCO_3$ (50 mL), brine, dried and solvent was evaporated. The crude material was chromatographed over silica gel using ethyl acetate/hexane (8:2) solvent to give compound (2*S*)-N-{4-[3'-(4"-acridonylcarboxamido)-propyl]-oxy-5-methoxy-2-nitro-benzoyl} pyrrolidine-2-carboxaldehyde diethyl thioacetal II as a yellow liquid.

^1H NMR ($CDCl_3$) δ 1.20-1.50 (m, 6H), 1.60-2.20 (m, 6H), 2.60-2.80 (m, 4H), 3.10-3.3 (m, 2H), 3.65-3.8 (m, 5H), 4.20-4.30 (m, 2H), 4.55-4.70 (m, 1H), 4.8 (d, 1H), 6.75 (s, 1H), 7.15

(t, 1H), 7.25 (t, 1H), 7.35 (d, 1H), 7.50 (s, 1H), 7.58-7.63 (t, 1H), 7.9 (bs, 1H), 8.15 (d, 1H), 8.35 (d, 1H), 8.55 (d, 1H); 12.3 (bs, 1H), MS (FAB) 679 $[M + H]^+$.

The compound (2*S*)-N-{4-[3'-(4"-acridonylcarboxamido)-propyl]-oxy-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal II (0.678 g, 1 mmol) was dissolved in methanol (15 mL) and added $SnCl_2.2H_2O$ (1.128 g, 5 mmol) was refluxed for 2 h or until the TLC indicated that reaction was completed. The reaction mixture was then adjusted to pH 8 carefully with saturated $NaHCO_3$ solution, diluted with ethyl acetate, filtered through celite and extracted. The combined organic phase was dried over Na_2SO_4, and evaporated under vacuum to afford crude (2*S*)-N-{4-[3'-(4"-acridonylcarboxamido)-propyl]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal III.

^1H NMR ($CDCl_3$) δ 1.20-1.45 (m, 6H), 1.55-2.35 (m, 6H), 2.60-2.85 (m, 6H), 3.6 (s, 3H), 3.7-3.8 (m, 2H), 4.15-4.25 (m, 2H), 4.62-4.75 (m, 2H), 6.25 (s, 1H), 6.8 (s, 1H), 7.15-7.3 (m, 2H), 7.35 (d, 1H), 7.65-7.70 (t, 1H), 7.85 (bs, 1H), 8.05 (d, 1H), 8.35 (d, 1H), 8.65 (d, 1H); 12.3 (bs, 1H).

A solution of compound (2*S*)-N-{4-[3'-(4"-acridonylcarboxamido)-propyl]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal III (0.648 g, 1 mmol), $HgCl_2$ (0.8145 g, 3 mmol) and $CaCO_3$ (0.3 g, 3 mmol) in MeCN-water (4:1) was stirred slowly at room temperature until TLC indicates complete loss of starting material. The reaction mixture was diluted with EtOAc (30 mL) and filtered through a celite bed. The clear yellow organic supernatant was extracted with saturated 5% $NaHCO_3$ (20 mL), brine (20 mL) and the combined organic phase is dried (Na_2SO_4). The organic layer was evaporated in vacuum and purified by column chromatography (90% CH_2Cl_2-MeOH) to give compound 7-methoxy-8-[3'-(4"-acridonylcarboxamido)propyl]-oxy-(11a*S*)1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one.

^1H NMR ($CDCl_3$) δ 1.20-1.30 (m, 2H), 1.85-2.40 (m, 6H), 3.5-3.8 (m, 6H), 4.20-4.30 (m, 2H), 6.80 (s, 1H), 7.2-7.35 (m, 2H) 7.40 (d, 1H), 7.5 (s, 1H), 7.65 (d, 1H), 7.75 (t, 1H), 8.05 (d, 1H), 8.45 (d, 1H), 8.65 (d, 1H); 12.25 (bs, 1H), MS (FAB) 525 $[M + H]^+$.

Example 4

Compound acridone acid (0.239 g, 1 mmol) was taken in dry DMF (10 mL), EDCI (0.203 g, 1.5 mmol)and HOBt (0.288 g, 1.5mmol) was added and the mixture was cooled at 0-5 °C and the mixture was stirred for 30 min. A solution of (4*R*)-hydroxy-(2*S*)-N-[4-(3'-aminopropyl)-oxy-5-methoxy-2-nitrobenzoyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula I (0.473 g, 5 mmol) in DMF was added to it at the same temperature and the solution was stirred at room temperature for overnight. The mixture was washed with

saturated $NaHCO_3$ (50 mL), brine, dried and solvent was evaporated. The crude material was chromatographed over silica gel using ethyl acetate/hexane (8:2) solvent to give (4*R*)-hydroxy-(2*S*)-N-{4-[3'-(4"-acridonylcarboxamido)-propyl]-oxy-5-methoxy-2-nitrobenzoyl} pyrrolidine-2-carboxaldehyde diethyl thioacetal II as a yellow liquid.

The compound (4*R*)-hydroxy-(2*S*)-N-{4-[3'-(4"-acridonylcarboxamido)-propyl]-oxy-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal II (0.694 g, 1 mmol) was dissolved in methanol (15 mL) and added $SnCl_2.2H_2O$ (1.128 g, 5 mmol) was refluxed for 2 h or until the TLC indicated that reaction was completed. The reaction mixture was then adjusted to pH 8 carefully with saturated $NaHCO_3$ solution, diluted with ethyl acetate, filtered through celite and extracted. The combined organic phase was dried over Na_2SO_4, and evaporated under vacuum to afford the crude compound (4*R*)-hydroxy-(2*S*)-N-{4-[3'-(4"-acridonylcarboxamido)-propyl]-oxy-5-methoxy-2-aminobenzoyl}pyrro-lidine-2-carboxaldehyde diethyl thioacetal III.

A solution of compound (4*R*)-hydroxy-(2*S*)-N-{4-[3'-(4"-acridonylcarboxamido)-propyl]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal III (0.664 g, 1 mmol), $HgCl_2$ (0.8145 g, 3 mmol) and $CaCO_3$ (0.3 g, 3 mmol) in MeCN-water (4:1) was stirred slowly at room temperature until TLC indicates complete loss of starting material. The reaction mixture was diluted with EtOAc (30 mL) and filtered through a celite bed. The clear yellow organic supernatant was extracted with saturated 5% $NaHCO_3$ (20 mL), brine (20 mL) and the combined organic phase is dried (Na_2SO_4). The organic layer was evaporated in vacuum and purified by column chromatography (90% CH_2Cl_2-MeOH) to give compound 7-methoxy-8-[3'-(4"-acridonyl carboxamido) propyl]-oxy-(4*R*)-hydroxy-(11a*S*) 1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiaze pin-5-one.

Example 5

Compound acridine acid (0.223 g, 1 mmol) was taken in dry DMF (10 mL), EDCI (0.203 g, 1.5 mmol)and HOBt (0.288 g, 1.5mmol) was added and the mixture was cooled at 0-5°C and the mixture was stirred for 30 min. A solution of (2*S*)-N-[4-(2'-aminoethyl)-oxy-5-methoxy-2-nitrobenzoyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula I (0.443 g, 1mmol) in DMF was added to it at the same temperature and the solution was stirred at room temperature for overnight. The mixture was washed with saturated $NaHCO_3$ (50 mL), brine, dried and solvent was evaporated. The crude material was chromatographed over silica gel using ethyl acetate/hexane (8:2) solvent to give compound (2*S*)-N-{4-[2'-(4"-acridinylcarboxamido)-ethyl]-oxy-5-methoxy-2-nitrobenzo-yl}pyrrolidine-2-carboxaldehyde diethyl thioacetal II as a yellow liquid.

The compound (2*S*)-N-{4-[2'-(4"-acridinylcarboxamido)-ethyl]-oxy-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal II (0.648 g, 1 mmol) was dissolved in methanol (15 mL) and added $SnCl_2.2H_2O$ (1.128 g, 5 mmol) was refluxed for 2 h or until the TLC indicated that reaction was completed. The reaction mixture was then adjusted to pH 8 carefully with saturated $NaHCO_3$ solution, diluted with ethyl acetate, filtered through celite and extracted. The combined organic phase was dried over Na_2SO_4, and evaporated under vacuum to afford the crude compound (2*S*)-N-{4-[2'-(4"-acridinylcarboxamido)-ethyl]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal III.

A solution of compound (2*S*)-N-{4-[2'-(4"-acridinylcarboxamido)-ethyl]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal III (0.618 g, 1 mmol), $HgCl_2$ (0.8145 g, 3 mmol) and $CaCO_3$ (0.3 g, 3 mmol) in MeCN-water (4:1) was stirred slowly at room temperature until TLC indicates complete loss of starting material. The reaction mixture was diluted with EtOAc (30 mL) and filtered through a celite bed. The clear yellow organic supernatant was extracted with saturated 5% $NaHCO_3$ (20 mL), brine (20 mL) and the combined organic phase is dried (Na_2SO_4). The organic layer was evaporated in vacuum and purified by column chromatography (90% CH_2Cl_2-MeOH) to give compound 7-methoxy-8-[2'-(4"-acridinylcarboxamido)ethyl]-oxy-(11a*S*)1,2,3,11a-tetrahydro-5*H*-pyrrolo [2,1-*c*][1,4]benzodiazepin-5-one.

Example 6

Compound acridine acid (0.223 g, 1 mmol) was taken in dry DMF (10 mL), EDCI (0.203 g, 1.5 mmol)and HOBt (0.288 g, 1.5mmol) was added and the mixture was cooled at 0-5 °C and the mixture was stirred for 30 min. A solution of (4*R*)-hydroxy-(2*S*)-N-[4-(2'-aminoethyl)-oxy-5-methoxy-2-nitrobenzoyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula I (0.459 g, 1 mmol) in DMF was added to it at the same temperature and the solution was stirred at room temperature for overnight. The mixture was washed with saturated $NaHCO_3$ (50 mL), brine, dried and solvent was evaporated. The crude material was chromatographed over silica gel using ethyl acetate/hexane (8:2) solvent to give (4*R*)-hydroxy-(2*S*)-N-{4-[2'-(4"-acridinylcarboxamido)-ethyl]-oxy-5-methoxy-2-nitrobenzoyl} pyrrolidine-2-carboxaldehyde diethyl thioacetal II as a yellow liquid.

The compound (4*R*)-hydroxy-(2*S*)-N-{4-[2'-(4"-acridinylcarboxamido)-ethyl]-oxy-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal II (0.664 g, 1 mmol) was dissolved in methanol (15 mL) and added $SnCl_2.2H_2O$ (1.128 g, 5 mmol) was refluxed for 2 h or until the TLC indicated that reaction was completed. The reaction mixture

was then adjusted to pH 8 carefully with saturated $NaHCO_3$ solution, diluted with ethyl acetate, filtered through celite and extracted. The combined organic phase was dried over Na_2SO_4, and evaporated under vacuum to afford the crude compound (4*R*)-hydroxy-(2*S*)-N-{4-[2'-(4"-acridinylcarboxamido)-ethyl]-oxy-5-methoxy-2-aminobenzoyl}pyrro-lidine-2-carboxaldehyde diethyl thioacetal III.

A solution of compound (4*R*)-hydroxy-(2*S*)-N-{4-[2'-(4"-acridinylcarboxamido)-ethyl]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal III (0.634 g, 1 mmol), $HgCl_2$ (0.8145 g, 3 mmol) and $CaCO_3$ (0.3 g, 3 mmol) in MeCN-water (4:1) was stirred slowly at room temperature until TLC indicates complete loss of starting material. The reaction mixture was diluted with EtOAc (30 mL) and filtered through a celite bed. The clear yellow organic supernatant was extracted with saturated 5% $NaHCO_3$ (20 mL), brine (20 mL) and the combined organic phase is dried (Na_2SO_4). The organic layer was evaporated in vacuum and purified by column chromatography (90% CH_2Cl_2-MeOH) to give compound 7-methoxy-8-[2'-(4"-acridinylcarboxamido)-ethyl]-oxy-(4*R*)-hydroxy-(11a*S*) 1,2,3,-11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiaze-pin-5-one.

Example 7

Compound acridine acid (0.223 g, 1 mmol) was taken in dry DMF (10 mL), EDCI (0.203 g, 1.5 mmol)and HOBt (0.288 g, 1.5mmol) was added and the mixture was cooled at 0-5 °C and the mixture was stirred for 30 min. A solution of (2*S*)-N-[4-(3'-amino-propyl)oxy-5-methoxy-2-nitrobenzoyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula I (0.457 g, 1 mmol) in DMF was added to it at same temperature and the solution was stirred at room temperature for overnight. The mixture was washed with saturated $NaHCO_3$ (50 mL), brine, dried and solvent was evaporated. The crude material was chromatographed over silica gel using ethyl acetate/hexane (8:2) solvent to give (2*S*)-N-{4-[2'-(4"-acridinylcarboxamido)-propyl]-oxy-5-methoxy-2-nitroben-zoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal II as a yellow liquid.

^1H NMR ($CDCl_3$) δ 1.20-1.50 (m, 6H), 1.60-2.40 (m, 6H), 2.60-2.85 (m, 4H), 3.10-3.25 (m, 2H), 3.85-3.9 (m, 5H), 4.20-4.30 (m, 2H), 4.65-4.70 (m, 1H), 4.82 (d, 1H), 6.8(s, 1H), 7.4-7.8 (m, 4H), 7.85-8.05 (t, 2H), 8.10 (d, 1H), 8.82 (s, 1H), 8.95 (d, 1H); 11.9(bs, 1H), MS (FAB) 663 $[M + H]^+$.

The compound (2*S*)-N-{4-[3'-(4"-acridinylcarboxamido)-propyl]-oxy-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal II (0.662 g, 1 mmol) was dissolved in methanol (15 mL) and added $SnCl_2.2H_2O$ (1.128 g, 5 mmol) was refluxed for 2 h or until the TLC indicated that reaction was completed. The reaction mixture was then

adjusted to pH 8 carefully with saturated $NaHCO_3$ solution, diluted with ethyl acetate, filtered through celite and extracted. The combined organic phase was dried over Na_2SO_4, and evaporated under vacuum to afford the crude compound (2*S*)-N-{4-[3'-(4"-acridinylcarboxamido)-propyl]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal III.

^1H NMR ($CDCl_3$) δ 1.20-1.5 (m, 6H), 1.60-2.40 (m, 6H), 2.60-2.80 (m, 4H), 3.55-3.7 (m, 2H), 3.8 (s, 3H), 3.9-4.00 (m, 2H), 4.15-4.25 (m, 2H), 4.65-4.80 (m, 2H), 6.25 (s, 1H), 6.8 (s, 1H), 7.50-7.80 (m, 4H), 7.90-8.00 (m, 2H), 8.85 (s, 1H), 8.95 (d, 1H); 11.9 (bs, 1H).

A solution of compound (2*S*)-N-{4-[3-(4"-acridinylcarboxamido)-propyl]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal III (0.632 g, 1 mmol), $HgCl_2$ (0.8145 g, 3 mmol) and $CaCO_3$ (0.3 g, 3 mmol) in MeCN-water (4:1) was stirred slowly at room temperature until TLC indicates complete loss of starting material. The reaction mixture was diluted with EtOAc (30 mL) and filtered through a celite bed. The clear yellow organic supernatant was extracted with saturated 5% $NaHCO_3$ (20 mL), brine (20 mL) and the combined organic phase is dried (Na_2SO_4). The organic layer was evaporated in vacuum and purified by column chromatography (90% CH_2Cl_2-MeOH) to give compound 7-methoxy-8-[3'-(4"-acridinylcarboxamido)propyl]-oxy-(11a*S*)1,2,3,11a-tetrahydro-5*H*-pyrrolo [2,1-*c*][1,4]benzodiazepin-5-one.

^1H NMR ($CDCl_3$) δ 1.20-1.30 (m, 2H), 1.95-2.45 (m, 6H), 3.5-3.8 (m, 5H), 4.25-4.45 (m, 3H), 6.80 (s, 1H), 7.50-7.80 (m, 5H) 7.95-8.1 (m, 2H), 8.15 (d, 1H), 8.90 (s, 1H), 9.00 (d, 1H); 12.00 (bs, 1H), MS (FAB) 509 $[M + H]^+$.

Example 8

Compound acridine acid (0.223 g, 1 mmol) was taken in dry DMF (10 mL), (0.203 g, 1.5 mmol)and HOBt (0.288 g, 1.5mmol)was added and the mixture was cooled at 0-5 °C and the mixture was stirred for 30 min. A solution of (4*R*)-hydroxy-(2*S*)-N-[4-(3'-aminopropyl)-oxy-5-methoxy-2-nitrobenzoyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal of formula I(0.473 g, 5 mmol) in DMF was added to it at the same temperature and the solution was stirred at room temperature for overnight. The mixture was washed with saturated $NaHCO_3$ (50 mL), brine, dried and solvent was evaporated. The crude material was chromatographed over silica gel using ethyl acetate/hexane (8:2) solvent to give compound (4*R*)-hydroxy-(2*S*)-N-{4-[3'-(4"-acridinylcarboxamido)-propyl]-oxy-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal II as a yellow liquid.

The compound (4*R*)-hydroxy-(2*S*)-N-{4-[3'-(4"-acridinylcarboxamido)-propyl]-oxy-5-methoxy-2-nitrobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal II (0.678 g, 1

mmol) was dissolved in methanol (15 mL) and added $SnCl_2.2H_2O$ (1.128 g, 5 mmol) was refluxed for 2 h or until the TLC indicated that reaction was completed. The reaction mixture was then adjusted to pH 8 carefully with saturated $NaHCO_3$ solution, diluted with ethyl acetate, filtered through celite and extracted. The combined organic phase was dried over Na_2SO_4, and evaporated under vacuum to afford the crude compound (4*R*)-hydroxy-(2*S*)-N-{4-[3'-(4"-acridinylcarboxamido)-propyl]-oxy-5-methoxy-2-aminobenzoyl}pyrro-lidine-2-carboxaldehyde diethyl thioacetal III.

A solution of compound (4*R*)-hydroxy-(2*S*)-N-{4-[3'-(4"-acridinylcarboxamido)-propyl]-oxy-5-methoxy-2-aminobenzoyl}pyrrolidine-2-carboxaldehyde diethyl thioacetal III (0.648 g, 1 mmol), $HgCl_2$ (0.8145 g, 3 mmol) and $CaCO_3$ (0.3 g, 3 mmol) in MeCN-water (4:1) was stirred slowly at room temperature until TLC indicates complete loss of starting material. The reaction mixture was diluted with EtOAc (30 mL) and filtered through a celite bed. The clear yellow organic supernatant was extracted with saturated 5% $NaHCO_3$ (20 mL), brine (20 mL) and the combined organic phase is dried (Na_2SO_4). The organic layer was evaporated in vacuum and purified by column chromatography (90% CH_2Cl_2-MeOH) to give compound 7-methoxy-8-[3'-(4"-acridinyl carboxamido) propyl]-oxy-(4*R*)-hydroxy-(11a*S*) 1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*]-[1,4]-benzodia-zepin-5-one.

Biological Activity: *In vitro* biological activity studies were carried out at National Cancer Institute (USA).

Cytotoxicity: 7-methoxy-8-[3'-(4"-acridonylcarboxamido)propyl]-oxy-(11a*S*)1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one.of formula IV was evaluated for primary anti-cancer activity (**Table 1**) and *in vitro* against sixty human tumour cells derived from nine cancer types (leukemia, non-small-cell lung, colon, CNS, melanoma, ovarian, prostate, and breast cancer). For each compound, dose response curves for each cell line were measured at a minimum of five concentrations at 10 fold dilutions. A protocol of 48 h continuous drug exposure was used and a sulforhodamine B (SRB) protein assay was used to estimate cell viability or growth. The concentration causing 50% cell growth inhibition (GI50), total cell growth inhibition (TGI, 0% growth) and 50% cell death (LC50, -50% growth) compared with the control was calculated. The mean graph midpoint values of log_{10}TGI and log_{10}LC50 as well as log_{10} GI50 for IV are listed in **Table 2**. The mean graph itself is shown in **Table 4.** As demonstrated by mean graph pattern, compound IV exhibits an interesting profile of activity and selectivity for various cell lines. The mean graph mid point of log_{10} TGI and log_{10} LC50 showed similar pattern to the log_{10} GI50 mean graph mid points.

Table 1. *In vitro* one dose primary anticancer assay[a] acridone linked PBD hybrid of IV

PBD hybrid	Growth percentages		
	(Lung) NCI-H460	(Breast) MCF7	(CNS) SF-268
IV	0	0	10

[a]One dose of IV at 10^{-4} molar concentration

The novel pyrrolobenzodiazepine hybrid 7-methoxy-8-[3'-(4"-acridonylcarboxamido)-propyl]-oxy-(11a*S*)1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one.of formula IV has shown to possess <10 nano molar potency (at the LC_{50} level) against one melanoma cancer (UACC-62) and 0.1 micro molar potency against colon cancer (HCC-2998), CNS cancer (SNB-75), breast cancer (MDA-MB-435) and also have <10 micro molar potency against two melanoma cancer cell lines (LOXIMVI, M14) and one renal cancer (SN12C). The LC_{50} values of nine cancers (average of six to nine cancer cell lines) of compound 7-methoxy-8-[3'-(4"-acridonylcarboxamido)-propyl]-oxy-(11a*S*)1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one.of formula IV listed in **Table 3**.

Table 2. log_{10} GI50 log_{10} TGI and log_{10} LC50 mean graphs midpoints(MG_MID) of in vitro cytotoxicity data for the compound IV against human tumour cell lines.

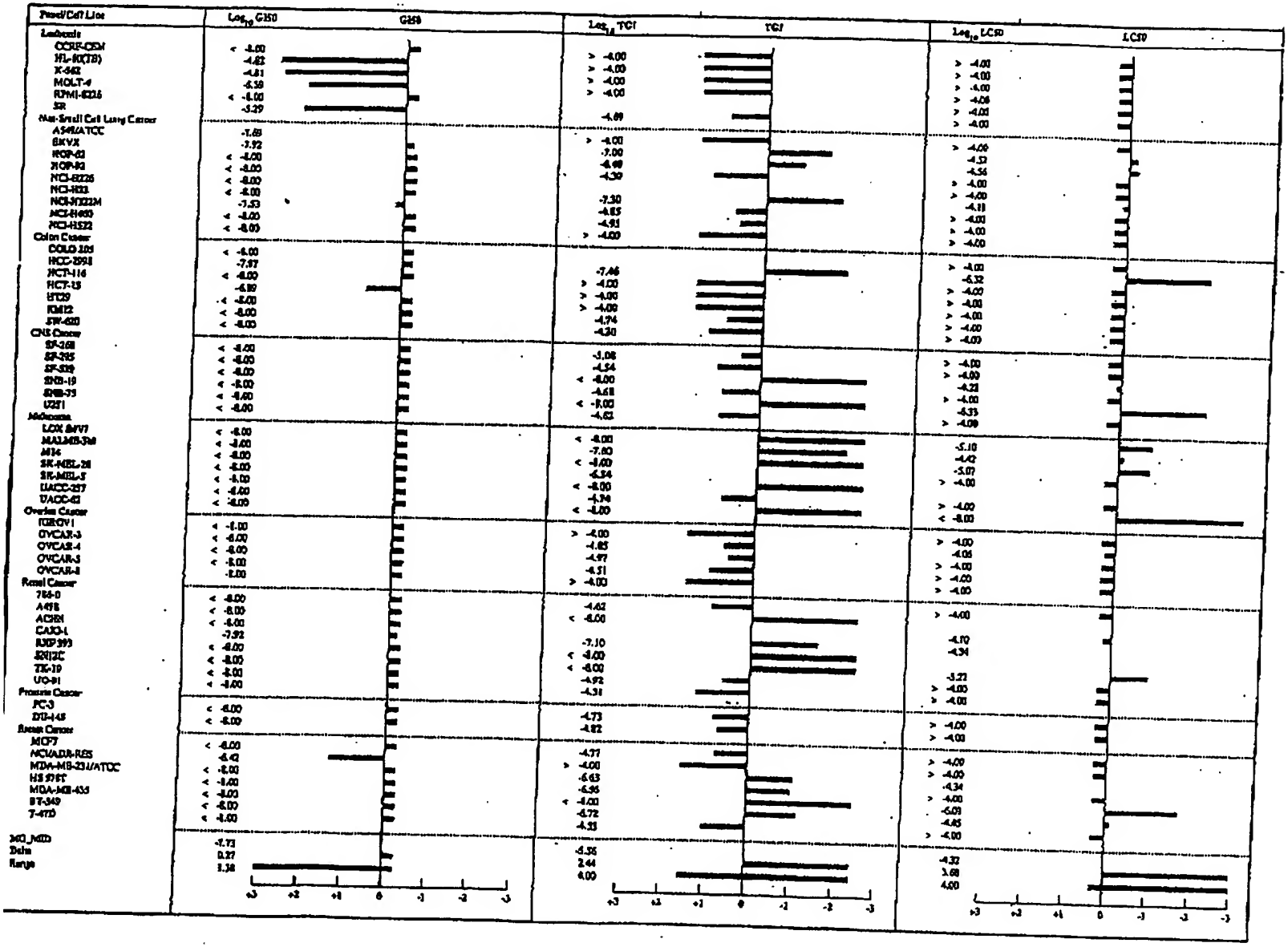
Compound	Log_{10} GI50	Log_{10} TGI	Log_{10} LC50
IV	-7.73	-5.56	-4.32

Table 3. Log LC50 (concentration in mol/L causing 50% lethality) Values for Compounds IV

Cancer	Compound IV
Leukemia	-4.00
non-small-cell lung	-4.14
Colon	-4.33
CNS	-4.425
Melanoma	-5.09
Ovarian	-4.012
Renal	-4.27
Prostate	-4.00
Breast	-4.40

Each cancer type represents the average of six to nine different cancer cell lines.

MEAN GRAPH


Panel/Cell Line
Log10 GI50
GI50
Log10 TGI
TGI
Log10 LC50
LC50
Leukemia
CCRF-CEM
HL-60(TB)
K-562
MOLT-4
RPMI-8226
SR
Non-Small Cell Lung Cancer
A549/ATCC
EKVX
HOP-62
HOP-92
NCI-H226
NCI-H23
NCI-H322M
NCI-H460
NCI-H522
Colon Cancer
COLO 205
HCC-2998
HCT-116
HCT-15
HT29
KM12
SW-620
CNS Cancer
SF-268
SF-295
SF-539
SNB-19
SNB-75
U251
Melanoma
LOX IMVI
MALME-3M
M14
SK-MEL-28
SK-MEL-5
UACC-257
UACC-62
Ovarian Cancer
IGROV1
OVCAR-3
OVCAR-4
OVCAR-5
OVCAR-8
Renal Cancer
786-0
A498
ACHN
CAKI-1
RXF 393
SN12C
TK-10
UO-31
Prostate Cancer
PC-3
DU-145
Breast Cancer
MCF7
NCI/ADR-RES
MDA-MB-231/ATCC
HS 578T
MDA-MB-435
BT-549
T-47D
MG_MID
Delta
Range